AMENDMENTS TO THE SPECIFICATION

At page 2, please replace the paragraph starting at line 25 with the following paragraph:

One of the peptide epitopes disclosed in WO00/26249 is RMFPNAPYL (SEQ ID NO: 1) (which we have also termed pWT126), and we have previously described a CTL which is able to: kill HLA-A2-positive targets coated with the WT1-derived peptide pWT126 (Gao et al (2000) *Blood* 95, 2198-2203); kill fresh HLA-A2-positive leukaemia cells expressing WT1 (Gao et al (2000) *Blood* 95, 2198-2203); kill HLA-A2-positive leukemia CFU progenitor cells (Gao et al (2000) *Blood* 95, 2198-2203; Bellantuono et al (2002) Blood 100, 3835-3837); kill HLA-A2-positive leukaemia LTC-IC stem cells (Bellantuono et al (2002) *Blood* 100, 3835-3837); kill HLA-A2-positive NOD/SCID leukaemia initiating cells (Gao et al (2003) *Transplantation* 75, 1429-1436); and do not kill normal HLA-A2-positive NOD/SCID engrafting hematopoietic stem cells (Gao et al (2003) *Transplantation* 75, 1429-1436). However, none of these publications give molecular information concerning the TCR present in the CTL, and the particular CTL line mentioned in the publications has not been made available to the public in any way and so the structure of the TCR is unknown and could not be derived by the skilled person (since the CTL line was not publicly available).

At page 3, replace the paragraph starting at line 10 with the following paragraph:

The present inventors have now cloned a TCR that is specific to RMFPNAPYL (SEQ ID NO: 1), a peptide of WT1 which is presented by HLA-A2 class I molecules, and have shown that introducing the TCR into either CD4-positive or CD8-positive T cells confers on the engineered T cells the ability to kill cancer cells which express WT1 endogenously. In addition, the inventors have defined the molecular structure of the TCR, identified the complementarity determining regions (CDRs), and describe how to make recombinant TCRs which are believed to retain the same specificity of the parent molecule.

At page 5, replace the paragraph starting at line 10 through line 24 with the following paragraph:

A first aspect of the invention provides a T cell receptor (TCR) molecule containing an alpha chain portion and a beta chain portion wherein the alpha chain portion contains three complementarity determining regions (CDRs):

CDR1α: SSYSPS (SEQ ID NO: 2)

CDR2α: YTSAATL (SEQ ID NO: 3)

CDR3α: VVSPFSGGGADGLT (SEQ ID NO: 4) or comprising or consisting of SPFSGGGADGLT (SEQ ID NO: 5) and the beta chain portion contains three complementarity determining regions (CDRs):

CDR1β: DFQATT (SEQ ID NO: 6)

CDR2β: SNEGSKA (SEQ ID NO: 7)

CDR3β: comprising SARDGGEG (SEQ ID NO: 8), or comprising or consisting of RDGGEGSETQY (SEQ ID NO: 9) or wherein up to three amino acid residues in one or more of the CDRs are replaced by another amino acid residue.

At page 5, replace the paragraph starting at line 31 through page 6, line 2 with the following paragraph:

Thus, in one embodiment using the IMGT system CDR3α may have the amino acid sequence VVSPFSGGGADGLT (SEQ ID NO: 4)and the constant portion includes the framework amino acid sequence FGKGTHLIIQP (SEQ ID NO: 10) (see Figure 5).

At page 6, replace the paragraph starting at line 4 with the following paragraph:

In another embodiment, using the Garcia nomenclature system (Garcia et al (1999) Ann. Rev. Immunol. 17, 369-397, incorporated herein by reference) CDR3α comprises or consists of the amino acid sequence SPFSGGGADGLT (SEQ ID NO: 5), the framework region immediately C-terminal to this has the amino acid sequence FGKGTHLIIQP (SEQ ID NO: 10) and the constant region begins with the amino acid sequence YIQNP (SEQ ID NO: 11) . . . (see Figure 5).

At page 6, replace the paragraph starting at line 11 with the following paragraph:

In one embodiment using the IMGT nomenclature system, CDR3β may have the amino acid sequence SARDGGEG (SEQ ID NO: 8)and the constant region immediately C-terminal to this includes the framework amino acid sequence SETQY (SEQ ID NO: 12) . . . (Figure 4).

At page 6, replace the paragraph starting at line 16 with the following paragraph:

In another embodiment, using the Garcia nomenclature system as above, CDR3β comprises or consists of the amino acid sequence RDGGEGSETQY (SEQ ID NO: 9) and the framework region immediately C-terminal to this has the amino acid sequence FGPGTRLLVL (SEQ ID NO: 13) and the immediately C-terminal constant region begins with the amino acid sequence EDLKN (SEQ ID NO: 14) . . . (see Figure 6).

At page 6, replace the paragraph starting at line 31 through page 7 line 3 with the following paragraph:

By "TCR molecule" we include any molecule which contains the given CDRs and also contains FRs suitably situated within the molecule so that the CDRs form a recognition site (combining site) which is able to bind to HLA-A2 presenting the peptide RMFPNAPYL (SEQ ID NO: 1) (ie a HLA-A2/RMFPNAPYL (SEQ ID NO: 1) complex).

At page 7, replace the paragraph starting at line 31 through page 8 line 4 with the following paragraph:

Typically, T cells expressing the TCR molecule recognise the HLA-A2 presenting peptide RMFPNAPYL (SEQ ID NO: 1) with substantially the same avidity as the TCR molecule which consists of the alpha and beta chains as described in Figures 2 and 4. This can be measured by retroviral-mediated transfer of the TCR into T cells followed by peptide titration experiments with the TCR-transduced T cells as outlined, for example, in Gao et al (2000) *Blood* 95, 2198-2203.

At page 13, replace the paragraph starting at line 16 through page 14, line 10 with the following paragraph:

As discussed above, TCR molecules in which one or more of the CDRs differ in sequence from the precise CDR sequences given in Figures 2 and 4 form part of the invention. Preferably, such TCR molecules are able to recognise the HLA-A2/RMFPNAPYL (SEQ ID NO: 1) complex more effectively than a TCR molecule with the precise CDR sequences. Thus, a further aspect of the invention provides a method of selecting a TCR molecule with improved binding to an HLA-A2/RMFPNAPYL (SEQ ID NO: 1) complex comprising (a) providing a TCR molecule containing an alpha chain portion and a beta chain portion wherein the alpha chain portion contains three complementarity determining regions (CDRs):

CDR1α: SSYSPS (SEQ ID NO: 2)

CDR2α: YTSAATL (SEQ ID NO: 3)

CDR3α: VVSPFSGGGADGLT (SEQ ID NO: 4) or comprising or consisting of SPFSGGGADGLT (SEQ ID NO: 5) and the beta chain portion contains three complementarity determining regions (CDRs):

CDR1β: DFQATT (SEQ ID NO: 6)

CDR2β: SNEGSKA (SEQ ID NO: 7)

CDR3β: comprising SARDGGEG (SEQ ID NO: 8) or comprising or consisting of RDGGEGSETQY (SEQ ID NO: 9) wherein at least one amino acid residue in one or more of the CDRs as given is replaced with another amino acid residue, (b) determining whether the TCR molecule binds to an HLA-A2/RFMPNAPYL (SEQ ID NO: 1)complex with greater affinity than a TCR molecule without the replacement amino acid(s), and (c) selecting a molecule which binds with greater affinity. Preferably, the CDR3β has the amino acid sequence given above in relation to the first aspect of the invention.

At page 14, replace the paragraph starting at line 11 with the following paragraph:

TCR molecules with altered CDRs can readily be made by protein engineering methods. For example, a TCR display library may be made in which the alpha chain and/or

beta chain CDR regions are mutagenised and the TCR molecules displayed using retroviral transduction on the surface of a T cell lymphoma (see Kessels et al (2000) Proc. Natl. Acad. Sci. USA 97, 14578-14583), or on the surface of a yeast or a bacteriophage. A HLA-A2/RMPNAPYL (SEQ ID NO: 1) complex may be used to select cells or bacteriophages which bind the complex with high affinity by virtue of the TCR molecule that they present. TCR molecules which have a higher binding affinity (lower K_D) than a TCR molecule with the precise CDR sequences are selected for further study.

At page 14, replace the paragraph starting at line 26 with the following paragraph:

Figure 1 shows the nucleotide coding sequence of the pWT126-specific TCR-alpha chain (Vα -1.5) (SEQ ID NO: 15).

At page 14, replace the paragraph starting at line 29 with the following paragraph:

Figure 2 shows the protein sequence of the pWT126-specific TCR-alpha chain (Vα -1.5). The position of the CDRs, FRs and constant region are marked. The leader sequence is shown in bold (SEQ ID NO: 16).

At page 15, replace the paragraph starting at line 1 with the following paragraph:

Figure 3 shows the nucleotide coding sequence of the pWT126-specific TCR-beta chain (Vβ -2.1) (SEQ ID NO: 17).

At page 15, replace the paragraph starting at line 4 with the following paragraph:

FIG. 4 shows the protein sequence of the pWT126-specific TCR-beta chain (V.beta.-2.1). The position of the CDRs, FRs and constant region are marked (SEQ ID NO: 18).

At page 15, replace the paragraph starting at line 7 with the following paragraph:

Figure 5 shows the same protein sequence as in Figure 2 (SEQ ID NO: 16) but the start position of the constant region is indicated to be in a different place. The CDR sequence

in this figure, starting after C, is based on IMGT nomenclature (primary sequence based). The Garcia nomenclature is based on structure and does not include the VV after the C (ie it starts SPF . . .). Va8.2 means variable alpha 8.2 gene segment and J45 means joining 45 gene segment.

At page 15, replace the paragraph starting at line 14 with the following paragraph:

Figure 6 shows the same protein sequence as in Figure 4 (SEQ ID NO: 18) except that CDR3β is indicated as being longer and the start position of the constant region is indicated to be in a different place. The CDR sequence in this figure, starting after C, is based on IMGT nomenclature (primary sequence based). The Garcia nomenclature is based on structure and does not include the SA after the C (ie it starts RDGG . . .). J2.5 refers to joining 2.5 gene segment.